III. Allowable Subject Matter

The Examiner stated in the Office Action that claim 8 would be allowable if rewritten in independent form, including all the limitations of the base claim and any intervening claims, and amended to read on the elected subject matter. The claim has been so amended, as indicated above.

IV. Rejections under 35 U.S.C. §112, Second Paragraph

Claim 7 was rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 has been amended, as noted above, to recite a 3'-to-3' linked nucleotide, as described in the specification.

Claims 6 and 8 were rejected as lacking proper antecedent basis. The terms at issue ("group" and "the segment") have been deleted from the claims.

In view of the foregoing, the applicants submit that the claims and specification, as amended, comply with the requirements of 35 U.S.C. §112, second paragraph.

V. Rejections under 35 U.S.C. §103

Claims 1-6 were rejected under 35 U.S.C. §103 as being unpatentable over Lamond *et al.* (*FEBS Letters* **325**(1,2):123-27, 1993), Kandimalla *et al.* (*Nucleosides & Nucleotides* **14**(3-5):1031-35, 1995), Ma *et al.* (*Biotech. Ann. Rev.* **5**:155-96, 2000), and Baracchini *et al.* (U.S. Patent No. 5,801,154). The rejection is respectfully traversed in light of the following remarks.

A. The Invention

The applicant's invention, as embodied in generic claim 1, is directed to a chimeric oligonucleotide having the formula 5'–W–X^1–Y–X^2–Z–3', where W represents a 5'-O-alkyl nucleotide, each of X^1 and X^2 represents a block of seven to twelve phosphodiester-linked 2'-O-alkyl ribonucleotides, Y represents a block of five to twelve phosphorothioate-linked deoxyribonucleotides, and Z represents a blocking group effective to block nuclease activity at the 3' end of the oligonucleotide.

B. The Cited Art

Lamond *et al.* describe synthetic 2'-O-alkyl ribonucleic acids made up entirely of phosphodiester-linked 2'-O-alkyl ribonucleotide subunits. (See, for example, title, abstract, and Fig. 1.) There is no teaching of any type of chimeric oligonucleotide. The oligomer contains no deoxyribonucleosides, modified or otherwise, no phosphorothioate linkages, and no 5' modification.

Kandimalla *et al.* describe a synthetic oligonucleotide (designated (**3**)) in which four of the five subunits at the 3' terminus are methylphosphonate-linked 2'-O-methyl ribonucleosides, and the remaining subunits are phosphodiester-linked (native) DNA (see Scheme 1 and lines 3-4 of page 1032). The oligomer contains no modified deoxyribonucleosides, no phosphorothioate linkages, no 5' modification, and apparently no 3' modification (the 3' terminal subunit is represented as d(T)).

Ma *et al.* was published in 2000. The present application has a priority date of August 27, 1999, the filing date of the provisional application, which has a disclosure substantially identical to that of the parent utility application filed on August 26, 2000. Accordingly, Ma *et al.* is not effective as prior art against the present application.

Baracchini *et al.* is directed to antisense strategies against multidrug ressistance-associated protein, or MRP. The reference describes a large number of possible oligonucleotide structural variations (columns 6-8), although the oligomers shown to be effective all have phosphorothioate backbones (Tables 1-4).

The reference discloses a series of chimeric antisense oligonucleotides (first four entries in Table 4, designated 13038-41), which are described at column 13, lines 15-26 and 35-50. Of these, compounds 13038 and 13039 have a central region of 12 deoxynucleotides, flanked on each side by 2'-methoxyethoxy ribonucleotides, and 13040 and 13041 have a central region of 8 deoxynucleotides, also flanked on each side by 2'-methoxyethoxy ribonucleotides. While compounds 13039 and 13041 have all-phosphorothioate (PS) backbones, 13038 and 13040 have terminal regions of four or six, respectively, phosphodiester (PO) linkages. The corresponding control-sequence oligomers are entries 6-9 in the Table, designated 13042-45.

The antisense efficacy of these oligonucleotides is described at column 13, lines 35-50 and illustrated in Figs. 1-4. It is clear from the Figures, and also concluded by the authors, that the

efficacy of the oligonucleotides was in the order 13039 > 13041 >> 13038 > 13040. The latter two compounds often gave results similar to the controls (see Figs. 1A-B and 3A-B). The former two compounds, as noted above, have backbones consisting entirely of phosphorothioate (PS) linkages, while the latter two compounds have terminal regions of four or six, respectively, phosphodiester (PO) linkages.

C. Analysis

Baracchini *et al.* disclose a series of chimeric oligonucleotides; the reference does not, however, show or suggest compounds having a central phosphorothioate-linked region flanked by regions of seven to twelve phosphodiester linkages. As described above, compounds 13038 and 13040 in Baracchini, having shorter flanking regions of phosphodiester linkages (four to six), gave results clearly inferior to their all-phosphorothioate counterparts in antisense assays. Such results would not motivate one skilled in the art to employ such compounds having any phosphodiester-linked flanking regions, much less longer flanking regions (eg. seven to twelve phosphodiester-linked ribonucleotides), as presently claimed.

The teachings of the other two effective cited references, as discussed above, either duplicate subject matter already found in Baracchini (e.g. the use of 2'-O-alkyl ribonucleotides, in Lamond) or have no relevance to the present claims (e.g. the use of methylphosphonate linkages in Kandimalla). Therefore, they do nothing to remedy the deficiencies of the Baracchini reference with respect to the present claims.

VI. Further Rejections under 35 U.S.C. §103

Claim 7 was rejected under 35 U.S.C. §103 as being unpatentable over Lamond *et al.*, Kandimalla *et al.*, Ma *et al.*, and Baracchini *et al.*, above, in view of Rosch *et al.* (U.S. Patent No. 5,750,669). The rejections are respectfully traversed in light of the following remarks.

A. The Invention

The applicant's invention, as embodied in claim 7, is directed to the composition of generic claim 1, comprising a chimeric oligonucleotide as described above, wherein the 3' terminal group Z is a 3'-to-3' linked nucleotide.

B. The Cited Art

Lamond *et al.*, Kandimalla *et al.*, Ma *et al.* and Baracchini *et al.* are discussed above. To

reiterate, Ma *et al.* is not effective as prior art against the present application. Baracchini actually teaches away from the use of flanking regions of 7 to 12 phosphodiester linkages in a phosphorothioate-linked oligonucleotide. Lamond and Kandimalla do not show a phosphorothioate-phosphodiester chimeric oligonucleotide at all; Lamond does not teach any kind of chimeric oligonucleotide; neither of these references teaches phosphorothioate linkages.

In addition, none of these references discloses or suggests a 3'-to-3' terminal nucleotide.

Rosch *et al.* describes the benefits of a terminal 3'-3' and/or 5'-5' internucleotide linkage in increasing stability of oligonucleotides against nucleases. The background of the patent describes problems that had been encountered with modified-backbone oligonucleotides designed to increase nuclease stability. Such problems included lack of specificity and the "chirality problem" in the widely used thiophosphate oligomers (another name for phosphorothioates) (column 2, lines 20-30); low solubility of uncharged analogs (column 2, lines 52-56); and difficult preparation and unpredictable behavior of various other analogs (paragraph bridging columns 2-3).

In contrast, the authors found that "this minimal structural modification" (i.e., the 3'-3' and/or 5'-5' terminal internucleotide linkage) "suffices to stabilize such components against nuclease degradation" (column 5, lines 21-23). Further, this "only slight structural modification results in a hybridization behavior which is almost identical to that of the biological oligonucleotides" (column 5, lines 24-26).

C. Analysis

Roche *et al.* disclose oligonucleotides having various linkages and having, in addition, a terminal 3'-3' and/or 5'-5' internucleotide linkage. As noted above, however, Roche *et al.* discusses the problems associated with modified backbone linkages (including phosphorothioates), and touts the benefits of modifying only the terminal groups of the oligonucleotide to achieve nuclease stability. In view of the overall teachings of the reference, one would not be motivated to selected a chimeric oligonucleotide backbone as claimed, having a central region of phosphorothioate linkages, to which to append a terminal 3'-3' or 5'-5' internucleotide linkage.

Even if such a terminal group were combined with the teachings of the references cited above, in particular Baracchini, the combined teachings would not motivate one skilled in the art

to prepare chimeric oligonucleotides having 7- to 12-mer flanking phosphodiester regions, for the reasons discussed above with respect to Baracchini.

VII. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

No fees are believed necessary with this communication. However, the Commissioner is hereby authorized and requested to charge any deficiency in fees herein, or credit any overpayment, to Deposit Account No. 50-0665.

Respectfully submitted,

Date: 10-31-01

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6. (Amended) The oligonucleotide of claim 1, wherein [group] Z is linked to X^2 via a linkage selected from the group consisting of a phosphotriester linkage, a phosphorothioate linkage, and a phosphoramidate linkage.

7. (Amended) The oligonucleotide of claim 1, wherein Z is a 3'-to-3' linked nucleotide.

8. (Amended) · [The oligonucleotide of claim 1] A chimeric oligonucleotide having the formula 5'–W–X^1–Y–X^2–Z–3', wherein

W represents a 5'-O-alkyl nucleotide;

each of X^1 and X^2 represents a block of seven to twelve phosphodiester-linked 2'-O-alkyl ribonucleotides;

Y represents a block of five to twelve phosphorothioate-linked deoxyribonucleotides; and

Z represents a blocking group effective to block nuclease activity at the 3' end of the oligonucleotide; and

[the segment] X^1—Y—X^2 has a nucleotide sequence selected from the group consisting of SEQ ID NOs: [1-24] 9 and 10.